Amendments to the Specification

At page 6, please amend the paragraph starting at line 10 as follows:

Figures ~~2A-2F~~ 2A-2E depict that P25 causes elevation of T668 phosphorylation of APP. (A) P25/Cdk5 transfected neurons display increased P-T668 staining. Primary cortical neurons were transfected with p25 and Cdk5. 24 hours after transfection, neurons were fixed and stained with (a) DAPI to show all nuclei in the field, (b) anti-p25 to show neurons transfected with p25, and (c) anti P-T668 to assay P-APP levels in neurons. Arrows indicate neurons that are transfected with p25/Cdk5, which are also the ones that display elevation of T668 phosphorylation on APP. (B-C) APP phosphorylation is increased in p25 Tg mice. (B) Immunohistochemical staining of the amygdala region of a brain section from a p25 Tg mouse using the P-T668 antibody showing strong cell bodies and neuropil immunoreactivity. (C) P-T668 staining on brain section from a WT littermate does not display any strong signal. Sections were counterstained with hematoxylin. (D) Enlargement of a p25Tg neuron with positive P-T668 staining. (E) Co-staining of P-T668 and the neuronal marker NeuN reveals that cells that accumulate P-T668 are neurons. ~~(F) Cdk5 phosphorylation of APP is induced by neurotoxic treatment. Primary hippocampal neurons were treated with 4 μM ionomycin and with no inhibitor, 20 μM butyrolactone, or 20 μM roscovitine for 5 hours. Neurons were lysed and assayed for the level of phosphorylated APP (top panel), total APP (middle panel), p35 and p35 (bottom panel).~~ Scale bars: 5 μM (A, D&E) and 25 μM (B, C).

At page 7, please amend the paragraph starting at line 24 as follows:

Figures ~~5A-5F~~ 5A-5E depict that phosphorylated APP localizes to endosome-like compartments in neurons from AD brains. (A) 100X DeltaVision deconvolution image showing no co-localization between T668 phosphorylated APP (green) and a synaptic vesicle marker (SV2 in red). (B) No co-localization was detected between T668 phosphorylated APP (green) and a lysosome marker (cathepsin D in red). (C) T668 phosphorylated APP (green) did not co-localize with an ER marker (gp96 in red). (D) T668 phosphorylated APP (green) co-localized with an endosome marker (Rab5 in red). (E) Phosphorylated APP (green) co-localized with ~~Rab4~~ BACE (red), an endosome marker. ~~(F) Phosphorylated APP (green) co-localized with EEA1 (red), another endosome marker.~~ Scale bars: 5 μM ~~(A-F)~~ (A-E).

At page 47, please amend the paragraph starting at line 10 as follows:

To determine the nature of the vesicular structures positive for P-APP, co-immunostaining was performed on AD hippocampal sections with a large panel of organelle markers. The staining results revealed that vesicular structures enriched in T668 phosphorylated APP were not synaptic vesicles (Fig. 5A), lysosomes (Fig. 5B) or part of the endoplasmic reticulum (ER) (Fig. 5C). Rather, the P-APP positive vesicles were labeled with the endosome markers Rab5 (Fig 5D), and BACE ~~Rab4~~ (Fig. 5E) ~~and EEA1 (Fig. 5F)~~, indicating that P-APP was enriched in the endocytic compartments in AD hippocampal neurons.

At page 47, please amend the paragraph staring at line 19 as follows:

To determine if neurotoxic conditions influence APP phosphorylation, primary hippocampal neurons were treated with ionomycin. Ionomycin, which induces conversion of p35 to p25, caused a marked elevation of T668 phosphorylation on APP ~~(Fig. 2F)~~. Two different Cdk-specific inhibitors, roscovitine and butyrolactone, inhibited T668 phosphorylation induced by ionomycin ~~(Fig. 2F)~~, indicating that APP is one of the Cdk5 targets whose phosphorylation is induced by neurotoxic conditions.